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ZORA URL: https://doi.org/10.5167/uzh-127106
Journal Article
Published Version

Originally published at:
Glaus, Toni M; Sigrist, Nadja; Hofer-Inteeworn, Nathalie; Kuemmerle-Fraune, C; Mueller, C; Geissweid, K; Beckmann, Katrin; Wenger, Michelle; Novo Matos, J (2016). Unexplained bleeding as primary clinical complaint in dogs infected with Angiostrongylus vasorum. Schweizer Archiv für Tierheilkunde, 158(10):701-709.
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# Unexplained bleeding as primary clinical complaint in dogs infected with *Angiostrongylus vasorum*

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DOI 10.17236/sat00088

Received: 06.05.2016
Accepted: 31.08.2016

## Summary

Unexplained bleeding was the primary clinical complaint in 15 dogs diagnosed with *A. vasorum* and was observed in the mouth, as external bleeding, as large subcutaneous hematoma, as hemoptysis, in the brain, post ovariectomy, as epistaxis, in the anterior ocular chamber and on a tracheal intubation tube. In 8 dogs the cause of bleeding initially was suspected to be a minor trauma or a surgical complication, and various surgical approaches had been undertaken to eliminate the problem. In only 3 dogs respiratory signs were observed before the bleeding prompted referral. The median time elapsed between the first recognized clinical signs attributed to *A. vasorum* until diagnosis was 2 weeks (range1 day to 4 months). Four dogs died, 3 on the day of admission and 1 dog 4 days after admission. Suspected causes of death were respiratory failure and cerebral hemorrhage in 2 dogs each. Four dogs had been pre-treated with NSAIDs; of these, 2 dogs developed severe hemoptysis (1 died), 1 dog developed brain hemorrhage (and died), and 1 dog developed a large subcutaneous hematoma with marked anemia. Bleeding at various sites may be the only recognized abnormality in *A. vasorum* infection. Without a high index of suspicion, the diagnosis and appropriate therapy may be delayed to the point of a fatal outcome. Tests of coagulation were quite variable and the cause of bleeding likely multifactorial.

**Keywords:** thrombocytopenia, thrombocytopathy, DIC, pulmonary hypertension, lymphocytosis

## Unerklärliche Blutung als primäres klinisches Leiden bei Hunden mit einer *Angiostrongylus vasorum* Infektion

Eine unerklärliche Blutung war das primäre klinische Leiden bei 15 Hunden mit einer anschliessenden Diagnose einer *A. vasorum* Infektion. Diese Blutungen wurden in der Maulhöhle, als äusserliche Blutungen, als grosse subkutane Hämatome, als Hämoptyse, als Hirnblutung, intraabdominal nach Ovariektomie, als Nasenbluten, in der vorderen Augenkammer und auf dem Trachealtubus zur Intubation beobachtet. Bei 8 Hunden wurde als Grund der Blutung initial ein kleines Trauma oder eine chirurgische Komplikation vermutet, und es waren verschiedene chirurgische Eingriffe zur Elimination des Problems unternommen worden. Nur bei 3 Hunden waren respiratorische Symptome bemerkt worden, bevor die Blutung zur Überweisung geführt hatte. Die mediane verstrichene Zeit zwischen der ersten durch *A. vasorum* verursachten klinischen Veränderung bis zur Diagnosestellung betrug 2 Wochen (1 Tag bis 4 Monate). Vier Hunde starben, 3 am Tag der Aufnahme und 1 Hund 4 Tage nach Aufnahme. Die vermuteten Todesursachen waren Atemversagen und Hirnblutung bei jeweils 2 Hunden. Vier Hunde waren mit einem NSAIA vorbehandelt worden; von diesen entwickelten 2 hochgradige Hämoptyse (1 starb), 1 Hund entwickelte eine Hirnblutung (und starb), und 1 Hund entwickelte ein grosses subkutanes Hämatom mit hochgradiger Anämie. Eine Blutung an einer beliebigen Stelle kann die einzige klinische Abnormalität bei einer *A.vasorum* Infektion sein. Ohne einen hohen Verdachtsmoment für diese Erkrankung kann die Diagnose und adäquate Behandlung soweit verzögert werden, dass der Ausgang letal ist. Der pathophysiologische Grund der Blutung ist wahrscheinlich multifaktoriell.

**Schlüsselwörter:** Thrombozytopenie, Thrombozytopathie, DIC, pulmonäre Hypertonie, Lymphozytose

## Introduction

*Angiostrongylus (A.) vasorum* is a metastrongylid with a wide geographic distribution infecting dogs and related canids (Bolt et al., 1994). The up to 25 mm long adult worms reside in pulmonary arteries and the right side of the heart. After a prepatence period of around 6–8 weeks, shedding of eggs starts in terminal pulmonary arteries (Rosen, 1970). Intense immune reactions against eggs and larvae elicit a severe inflammatory response in pulmonary arteries and the adjacent pulmonary parenchyma with coalescing granulomata, arterial thrombosis and bleeding (Prestwood et al., 1981; Mahaffey et al., 1981; Schnyder et al., 2010). Even though the existence of *A. vasorum* has long been recognized in Switzerland, (Eckert and Lämmler, 1972), until around 10 years ago it was not an important disease and the diagnosis was only rarely made both intra vitam and at necropsy. This has changed remarkably over the last decade, and the disease is now very commonly diagnosed. Besides increased veterinary practitioner awareness, factors underlying this trend could be effect of longterm climate change on intermediate host availability and/or parasite development rate, increasing dog movement, or increasing transmission through the fox population (Taylor et al., 2015).

The clinical course can range from very mild with minimal symptoms and spontaneous remission (Prestwood et al., 1981) to very severe with rapid deterioration from the first observed signs until death (Matos et al., 2016). Reasons for quite variable presentation may in part reflect quantity of infection, considering that clinical and radiographic abnormalities were more severe in heavier infected experimental dogs (Schnyder et al. 2010, Kranjc et al. 2010). However, there are probably other as important factors like repetitive infections and individual host immunity and immune response (Kranjc et al. 2010).

Furthermore, the organ manifestation can be quite variable (Bolt et al., 1994). In view of the parasite's typical primary localization in pulmonary arteries, expectedly the primary or most common clinical presentation is respiratory disease with cough or dyspnea. A subset of dogs with severe pulmonary vascular and parenchymal changes will present with signs of pulmonary hypertension rather than respiratory compromise. Therefore a second important clinical presentation is right-sided forward or backward heart failure with weakness, syncope and ascites (Glaus et al., 2010; Borgeat et al., 2015; Matos et al., 2016).

Besides the classic pulmonary (vascular) localization of this "heart worm" ectopic migration of larvae is also common. A third important organ manifestation is CNS disease with signs of meningitis and encephalitis, including seizures (Perry et al., 1991; Staebler et al., 2005; Denk et al., 2009). Some dogs may have ophthalmologic abnormalities (Rosenlund et al., 1991; King et al., 1994). Finally, a few dogs present with polyuria/polydipsia due to hypercalcemia, thought to be caused by excessive vitamin D production associated with granulomatous disease (Boag et al., 2005; Adamantos et al., 2015).

Considering the pathophysiology of this disease, i.e. vasculitis in arteries as a reaction against the eggs and larvae, hemostatic abnormalities are an expected consequence. Likewise, pulmonary thrombosis invariably has been found in experimentally and naturally infected dogs and is one explanation for the development of pulmonary hypertension (Prestwood et al., 1981; Kranjc et al., 2010; Matos et al., 2016). On the other side of the hemostasis spectrum, bleeding is an important part of the pathophysiologic changes in many dogs. It is found (upon necropsy) in the lungs as well as the CNS and eyes, depending on the localization of the primary disease process in the individual dog (Adamantos et al., 2015). We have seen several dogs where unexplained bleeding was the primary presenting complaint, in which *A. vasorum* infection was not considered initially. In some of these dogs the bleeding itself reached a life-threatening degree. In other dogs the underlying *A. vasorum* infection further evolved to a life threatening condition (e.g. respiratory failure) and even death. Therefore, it is the goal of this case series to characterize *A. vasorum* infected dogs with the primary complaint of unexplained bleeding.

## Material and methods

### Dogs

Records of dogs that were eventually diagnosed with *A. vasorum* and that were presented with the primary complaint of spontaneous or unexplained bleeding were analyzed with regard to the individual patients' clinical abnormalities, laboratory and imaging findings. The initial presentation and the course of the disease until *A. vasorum* was diagnosed were extracted from the clients' history. Between April 2011 and March 2016, *A. vasorum* infection was diagnosed in 15 dogs that had been presented with the primary complaint of spontaneous or unexplained bleeding. The sex distribution was 11 females and 4 males. Dogs of all ages were affected, but most were young (median age 15 months, range 6 months to 11 years). Most dogs were medium-sized (median 20 kg, range 4–39 kg). Twelve different breeds were represented of which Labrador Retrievers (n=3) and Siberian Huskies (n=2) were identified more than once.

**Table 1:** Clinical presentation, radiographic findings, diagnosis, therapy and outcome in 15 dogs with bleeding due to *A. vasorum*.

| | Dog | Presenting complaint | Previous signs | Respiratory signs | Thoracic rads, lung pattern | Dx# | Tx | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | Miniature Pinscher 10m, female 4 kg | Large unexplained hematoma ventral neck/ cranial shoulder | – | Dyspnea 3m after 1st bleeding | Mild generalized interstitial at time of hematoma | Snap + Baerm+ | Crystalloids Panacur$^{R}$ Prednisolone Viagra$^{R}$ Vetmedin$^{R}$ Plavix$^{R}$ | Severe PH and death on day presented with dyspnea |
| 2 | Mixed-breed, 10y, female 18 kg | Large unexplained peritarsal hematoma, marked anemia | 1w prev, lameness hind leg, Tx NSAID | None | Mild diffuse interstitial | Snap + Serol + | Ec conc, plasma Panacur$^{R}$ Prednisolone Cyklokapron$^{R}$ | Discharged after 7d, cured |
| 3 | Dalmatian 1.5y, female 19 kg | Large hematoma ventral neck/cranial shoulder due to suspected bite wound 3d prev | 3m prev, unusual bleeding at OE; 6w prev protracted bleeding from tongue | None | nd | Serol + | Doxycycline Panacur$^{R}$ | Discharged after 2d |
| 4 | Weimaraner 8m, female 23 kg | Ataxia, tetraplegia, nystagmus; suspected cerebral hemorrhage | 2w prev, sublingual bleeding, sutured, NSAID | Cough 10d after 1st bleeding | Interstitial diffuse, alveolar peripherally caudo-dorsally | Serol + | Crystalloids Panacur$^{R}$ Prednisolone Cyklokapron$^{R}$ | Death same day, suspected cerebral hemorrhage |
| 5 | English Bulldog 2y, male 36 kg | Bleeding from gums | 1d prev, played with brunch, blood in saliva | Cough same day as oral bleeding | Mild generalized interstitial | Smear + Serol + | Plasma Prednisolone Panacur$^{R}$ Cyklokapron$^{R}$ | Discharged after 2d, cured |
| 6 | Labrador 7y, female 25 kg | Large hematoma ventral neck | 4d prev, sublingual bleeding left, sutured; 2d prev same on the right, sutured | None | Mild generalized interstitial | Serol + | Crystalloids Vitamine $K_1$ Panacur$^{R}$ | Discharged after 3d, cured |
| 7 | Hovawart 6y, female 39 kg | Non-stoppable bleeding from lip | 1d prev, after playing with other dog bleeding from lip, sutured | Cough when excited for 3m | Mild nodular interstitial caudally | Baerm + Serol - | Plasma Panacur$^{R}$ Prednisolone Cyklokapron$^{R}$ | Discharged after 4d, cured |
| 8 | Rhodesian Ridgeback 11m, male 35 kg | Non-stoppable bleeding from tail | 1w prev, at tip of tail non stoppable bleeding; 4d prev, last tail vertebra removed | None | Mild interstitial and alveolar left caudally | Smear + Baerm + | Plasma Panacur$^{R}$ Prednisolone Cyklokapron$^{R}$ | Discharged after 4d, cured |
| 9 | Boxer 15m, female 25 kg | Epistaxis | 5w prev, bleeding paw after accident, sutured, still bleeding after 10d | None | Interstitial multifocal nodular, particularly caudodorsally | Baerm + Serol + | Crystalloids Vitamin $K_1$ Panacur$^{R}$ Prednisolone | Discharged after 6d, cured |
| 10 | Labrador 6m, male 20 kg | 15 seizures in last 24h, blood in endotracheal tube at anesthesia for CSF tap; CSF normal | Seizures for 3m | None | Interstitial nodular diffuse particularly at periphery | Serol + | Crystalloids Phenobarbital Advocate$^{R}$ Amoxi-Clav | Death after 4d |
| 11 | Golden Retriever, 1.5y, female 17 kg | Seizures, MRI consistent with cerebral hemorrhage; CSF xanthochromia and mixed inflammation* | 4m prev, unexplained severe bleeding after OE | None | Mild interstitial | Serol + | Panacur$^{R}$ Advocate$^{R}$ Prednisolone Amoxi-Clav | Discharged after 7d, cured |
| 12 | Irish Terrier 11y, female 21 kg | Progressive anemia, severe bleeding after OHE | 1w prev, OE, repeated surgery due to bleeding | None | Unremarkable | Baerm + | Panacur$^{R}$ Amoxi-Clav | Discharged after 7d, cured |
| 13 | Labrador 9m, female 20 kg | Severe hemoptysis | 2m prev, unilateral bleeding into anterior ocular chamber; 2d prev, cough | Cough 2m after ocular bleeding | Severe interstitial to alveolar in periphery | Serol + | Panacur$^{R}$ Prednisolone | Discharged after 5d, cured |
| 14 | Husky 8m, female 16 kg | Acute severe hemoptysis | 3w prev, cough, gone with cough sirup and NSAID | Cough 3w before hemoptysis | na | Snap + Smear + | Plasma Panacur$^{R}$ Prednisolone Cyklokapron$^{R}$ | Discharged after 3d, cured |
| 15 | Husky 8m, male 19 kg | Acute hemorrhagic "vomiting", also pouring through nares, shock | Vomiting since puppy, cough for 1m, pretreated with NSAID | Cough 1m before bleeding | Generalized severe interstitial, alveolar accessory and right cranial lobes | Smear + Serol + | Ec conc Crystalloids Panacur$^{R}$ Prednisolone | Death 5h after admission, profuse hemoptysis |

y, year; m, month; w, week; d, days; prev, previously; CSF, cerebrospinal fluid, *1.7 g/l protein, 132 cells/ul, mixed population, xanthochromia; OE, ovariectomy; Dx, diagnosis: #Serol, Antigen EIA (Schnyder et al. 2011); Snap, Angio Detect™ ; Baerm, Baermann coprology (Deplazes et al. 2013); smear, direct fecal smear examination by emergency doctor; Tx, therapy; nd, not done; na, not available; Ec conc, erythrocyte concentrate.

### Diagnosis and laboratory examinations

The diagnosis of *A. vasorum* was confirmed by direct fecal smear examination, fecal Baermann examination, antigen detection in serum (Schnyder et al., 2011) or a pet-side antigen test (Angio Detect™, Idexx Diavet AG, CH-Bäch). Automated hematological analyses were performed on a Sysmex XT 2000i (Sysmex digitana, CH-Horgen, except if indicated otherwise pocH-100iV Diff, Medical Solution GmbH, Ch-Hünenberg), biochemical analyses were performed on a Cobas 6000 (Cobas 6000. Roche Diagnostics AG, CH-Rotkreuz). Prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT) and fibrinogen (thrombin time Clauss method) were performed on a Diagnostica Stago (Diagnostica Stago, Roche Diagnostics AG, CH-Rotkreuz). The activated coagulation time (ACT) was performed on a Hemochron 401 (Hemochron 401, Fresenius AG, CH-Stans). Plasma D-Dimers were measured using an immunoturbidimetric method on a Cobas Integra Cobas Integra, Roche Diagnostics AG, CH-Rotkreuz). To measure the buccal mucosal bleeding time (BMBT) a standardized mucosal incision was made using a spring-loaded device (Surgicutt junior ITC, USA-Edison).

### Diagnostic imaging

Brain Magnet Resonance Tomography (MRI) was performed with a 3Tesla system (Ingenia 3T, Philips AG, CH-Zurich). Echocardiographic examination (Vivid 7, General Electrics, CH-Glattbrugg) to asses for pulmonary hypertension (PH) included qualitative 2-dimensional assessment, spectral Doppler measurements of tricuspid and pulmonic insufficiency peak velocities, and assessment of the pulmonary artery flow profile as described elsewhere (Glaus, 2015).

## Results

### Clinical presentation

The sites of bleeding were variable and in some dogs occurred in multiple locations (Table 1). In 8 dogs the cause of bleeding initially was suspected to be a non-specified minor trauma or a surgical complication and in these dogs various surgical approaches had been undertaken as an attempt to solve the problem. Four dogs had received a non-steroidal anti-inflammatory drug (NSAID) before the bleeding prompted referral. All individual clinical data are specified and detailed in Table 1. The median time elapsed between the first recognized clinical signs (retrospectively) attributed to *A. vasorum* until diagnosis was 2 weeks (range 1 day to 4 months); in only 2 dogs (both with profuse bleeding from the oral mucosa) *A. vasorum* was the prime suspect for the spontaneous bleeding.

Based on patient history, respiratory signs were absent in 8 dogs. In 3 dogs, cough or dyspnea were observed 10 days to 3 months after the first bleeding, and in 1 dog cough and dyspnea occurred concurrently with the bleeding (hemoptysis). In only 3 dogs cough was present before bleeding prompted referral; duration of cough was 1 to 3 months.

### Course of the disease

The course of disease was variable. After diagnosis, 11 dogs recovered quickly and uneventfully with antiparasitic and supportive therapy and were discharged after a median of 4 days (range 1–7 days). Four dogs died, 3 dogs on the day of admission and 1 dog 4 days after admission. These 4 dogs had shown signs likely caused by *A. vasorum* for 2 weeks to 3 months, and all were young (6–8 months). Suspected causes of death in 2 dogs each were respiratory failure (1 dog with severe PH, and 1 dog with severe hemoptysis) and cerebral hemorrhage. Of the 4 dogs that had been pre-treated with NSAIDs, 2 dogs were presented with severe hemoptysis (one died), 1 dog with brain hemorrhage (and died), and 1 dog with a peritarsal hematoma and marked anemia.

Treatments of the individual dogs are depicted in Table 1. The dosage for Fenbendazole (Panacur, MSD Animal Health GmbH, CH-Luzern) was 50 mg/kg/day for 21 days, for Prednisolone (Streuli, CH-Uznach) 1 mg/kg/day for 3–5 days, and for Tranexamic acid (Cyklokapron, MEDA Pharma GmbH, CH-Wangen) 20 mg/kg 3×/day for 1–3 days.

### Laboratory findings

Fifteen blood counts were obtained upon admission in 14 dogs (2 admissions 4 months apart in one dog). The individual results are shown detailed in Table 2. The median hematocrit was 31% (range 17–47%), and anemia was present in 11 of 15 dogs. Leukocytosis (mostly neutrophilic) was present in 12 of 15 dogs, but with one exception was only mild to moderate. A left shift was present in 5 of 13 samples, but remarkable only in one. Eosinophilia was present in 5 of 13, basophilia in 3 of 11, and monocytosis in 4 of 11 dogs. Only 1 dog showed lymphopenia, and 2 dogs showed lymphocytosis. Biochemichal profiles were mostly unremarkable. Only one dog showed mild hypoalbuminemia (25 g/l), and one dog showed hyperglobulinemia (56 g/l).

The median thrombocyte count was 118'000/ul (range 33'000–303'000/ul), and thrombocytopenia was present in 7 of 14 dogs. One or several coagulation times were obtained in 14 dogs. In most dogs, at least one time of coagulation was abnormal, however, coagulation times were mostly only mildly prolonged. Only one dog presented with all measured coagulation times in the nor-

mal range. The fibrinogen concentration was obtained in 8 dogs, and was below the detection limit in 4 of 8 dogs, normal in 3 of 8 dogs and increased in 1 of 8 dogs, D-dimers were measured in 3 dogs, and were elevated in 2 of these. The individual results of the coagulation tests are shown in Table 3.

The diagnosis of *A. vasorum* infection was confirmed serologically in 10 dogs, by pet-side antigen test in 3 dogs, by fecal Baermann exam in 5 dogs and by a direct fecal smear in 4 dogs. In 8 dogs multiple tests were performed. Disparity of the test results was found in only 1 dog with a positive fecal Baermann, but a negative serology result.

### Imaging findings

Thoracic radiographs were available for evaluation in 13 dogs. In 6 dogs, they were considered unremarkable or they showed only a mild interstitial pattern. In seven dogs, the radiographs showed peripherally pronounced interstitial to alveolar opacifications, typical for *A. vasorum* infection (table 1). Echocardiography was performed in 8 dogs at the time of bleeding and only one had evidence of pulmonary hypertension (PH, TR-PG 40 mmHg). In one additional dog severe PH was found 3 months after the unexplained bleeding had been observed. At this time bleeding was no longer detected.

## Discussion

Bleeding diathesis has long been recognized as one possible clinical manifestation in some dogs with *A. vasorum* infection (Boag et al., 1994), however, this fact is most apparently not broadly appreciated. With reference to our case series, in only 2 dogs *A. vasorum* was considered a potential cause already at the onset of the sometimes excessive bleeding. In the remaining dogs, bleeding initially was thought to be due to non-specified trauma or iatrogenic from surgery. In view of the risk of a fatal outcome, 4 of 15 dogs in our case series, a high index of suspicion for this disease is crucial. Unfortun-

**Table 2:** Hematologic findings in 15 dogs with spontaneous bleeding due to *A. vasorum* infection.

| | Dog | Hct [%] | Leuk [x10$^3$/ul] | Band [x10$^3$/ul] | Seg [x10$^3$/ul] | Eos [x10$^3$/ul] | Baso [x10$^3$/ul] | Mono [x10$^3$/ul] | Lymph [x10$^3$/ul] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Mini Pinscher 10 m ! | – | – | – | – | – | – | – | – |
| 2 | Mixed-breed 10y | 20 | 40.00 | 5.60 | 27.40 | 2.20 | 0 | 2.80 | 2.00 |
| 3 | Dalmatian 1.5y | 27 | 13.55 | 0 | 9.79 | 0.54 | 0.12 | 0.92 | 2.18 |
| 4 | Weimaraner 8m ! | 43 | 21.10 | 0 | 14.98 | 1.06 | 0 | 0.84 | 4.22 |
| 5 | English Bulldog 2y | 45 | 14.60 | 0 | 9.99 | 1.14 | 0.02 | 0.54 | 2.94 |
| 6 | Labrador 7y | 24 | 10.40[c] | 0 | 9.50[c] | 0.30[c] | [c] | [c] | 0.60[c] |
| 7 | Hovawart 6y | 36 | 10.90 | 0.05 | 5.43 | 2.17 | 0.54 | 0.54 | 2.12 |
| 8 | Ridgeback 11m | 31 | 26.10 | 0 | 14.52 | 1.91 | 0.04 | 1.57 | 8.04 |
| 9 | Boxer 15m | 43 | 19.20 | 0.29 | 16.84 | 0 | 0 | 0.38 | 1.73 |
| 10 | Labrador 6m ! | 47 | 19.80 | – | – | – | – | – | – |
| 11 | Golden Retriever, 1.5y | 32<br>40 | 21.70<br>15.80 | 0.11<br>0 | 17.79<br>11.13 | 0<br>0.63 | 0<br>0 | 1.95<br>0.87 | 1.84<br>3.16 |
| 12 | Irish Terrier 11y | 17 | 14.20 | 0.92 | 9.87 | 0.21 | 0 | 0.85 | 2.34 |
| 13 | Labrador 9m | 24 | 24.10 | 0.12 | 10.84 | 5.90 | 1.32 | 2.53 | 3.37 |
| 14 | Husky 8m | 21 | 23.900 | – | – | – | – | – | – |
| 15 | Husky 8m ! | 29 | 10.500[c] | 0 | 5.900[c] | 1.40[c] | [c] | [c] | 3.200[c] |
| | normal | 42–55 | 4.7–11.3 | <0.08 | 2.5–7.44 | 0.12–1.29 | 0–0.08 | 0.20–0.92 | 1.15–3.40 |

! dogs that died; [c] pocH-100iV Diff

ately, clinical signs, imaging findings and routine laboratory analyses may be quite unremarkable or non-specific. In only 4 dogs in this case series, respiratory signs that might raise the index of suspicion for an infection with pulmonary parasites, were present before or at the time of bleeding. Thoracic radiographs were suspicious for *A. vasorum* in only half of the dogs. Eosinophilia and basophilia, simple markers of parasitic disease, are commonly absent (Schnyder et al. 2010, Glaus et al., 2010). In the cases of this report, eosinophilia was present in only 5 of 13, and basophilia in 3 of 11 samples. A remarkable finding in the differential blood count was the lack of lymphopenia and even (marked) lymphocytosis in 2 cases despite severe stress of disease.

The often unremarkable thoracic radiographs may be explained in several ways. One explanation is the fact that thoracic radiographs may have poor sensitivity to detect pulmonary vascular pathology. Some dogs may develop severe PH despite quite unremarkable radiographs; however, these dogs have severe pulmonary damage visualized by CT and confirmed by histopathology (Matos et al. 2016). The more likely explanation is the absence of much pathological changes in the pulmonary vessels and adjacent parenchyma which is supported by the fact that many dogs did not show respiratory signs. Even though dogs of all ages were present in this study, most were young, and the ones with fatal outcome were the youngest. This is similar to dogs with *A. vasorum* induced PH, where the most severe PH with a fatal outcome more commonly occurred in younger dogs (Matos et al., 2016).

It is interesting to note that some dogs develop a life-threatening hypercoagulable and others a hypocoagulable state. In a subgroup of infected dogs, clinical signs are dominated by the underlying pulmonary (vascular) disease and associated pulmonary artery thrombosis. Typically, respiratory signs with cough and dyspnea and/or signs of cardiovascular insufficiency due to pulmonary hypertension dominate the clinical picture. Spontaneous or inappropriate bleeding is usually not present in these cases with the exception of hemoptysis in some. Furthermore, coagulation times are usually normal, in experimentally as well as naturally infected dogs (Schnyder et al., 2010, Glaus et al., 2010, Borgeat et al., 2015; Matos et al., 2016). In contrast, another subgroup of dogs mainly presents with clinical signs dominated by bleeding and, like in our case series, abnormal coagulation tests are usually present (Chapman et al., 2004, Adamantos et al., 2015).

The exact pathomechanism of bleeding in these dogs is not clearly established. Basically, one mechanism may be an abnormal primary hemostasis. Immune-mediated thrombocytopenia (ITP) has been described in one dog where low platelets were the suspected cause of bleeding (Gould and McInnes, 1999). In our dogs, thrombocytopenia was not considered an important underlying cause as platelet counts were above 30'000/ul in all dogs

**Table 3:** Coagulation parameters in 15 dogs with bleeding associated with *A. vasorum* infection.

| | Dog | Tc [x10$^3$/ul] | PT [sec] | PTT [sec] | TT [sec] | Fibrinogen [g/l] | D-Dimer [mg/l] | Other coagulation tests |
|---|---|---|---|---|---|---|---|---|
| 1 | Miniature Pinscher, 10m! | – | – | – | – | – | – | – |
| 2 | Mixed-breed, 10y | 42 | 10.2 | 17.4 | | 1.0 | – | – |
| 3 | Dalmatian, 1.5y | 61 | 7.8 | 12.9 | – | 1.1 | – | – |
| 4 | Weimaraner, 8m ! | 210 | 18.2 | 23.4 | 23.2 | <0.1 | – | – |
| 5 | English Bulldog, 2y | 134 | 16.0 | 16.9 | – | <0.1 | – | – |
| 6 | Labrador, 7y | 149 | 8.8 | 12.3 | – | – | – | BMBT 2'56'' ACT 2'54'' |
| 7 | Hovawart, 6y | 87 | 24.1 | 26.7 | 28.6 | <0.1 | 0.9 | |
| 8 | Rhodesian Ridgeback, 11m | 99 | 13.8 | 19.5 | – | <0.1 | – | – |
| 9 | Boxer, 15m | 96 | 10.7 | 16.3 | – | 1.0 | – | ACT 2'26'' |
| 10 | Labrador, 6m ! | 303 | – | – | – | – | – | BMBT 1'30'' |
| 11 | Golden Retriever, 1.5y | 226<br>157 | 8.5<br>7.8 | 14.0<br>12.5 | 16.8<br>14.1 | – | 0.4 | BMBT 1' |
| 12 | Irish Terrier, 11j | 202 | – | 14.8 | 15.9 | 8.7 | – | – |
| 13 | Labrador, 9m | 33 | 10.6 | 17.8 | – | | 1.5 | |
| 14 | Husky, 8m | clumped | – | – | – | – | – | – |
| 15 | Husky, 8m ! | 57 | – | – | – | – | – | ACT 2'26'' |
| | normal | 130–394 | 6.3–8.5 | 9.6–16.1 | 12.3–21.6 | 1.0–2.5 | 0–0.4 | |

! dogs that died; Tc, platelets; BMBT, buccal mucosal bleeding time, normal <4', Kraus and Johnson, 1989; ACT, activated coagulation time[f], normal <2', Glaus et al. 1996

(Scott and Jutkowitz, 2010), and half of the dogs had normal platelet counts. However, thrombocytopenia may have been a contributing factor in some. Abnormal platelet function is an additional possibility. The BMBT was normal in 3 dogs, not supporting the presence of a thrombopathy at least in these. Nevertheless, iatrogenic abnormal platelet function is one plausible factor in the 4 dogs that had received a NSAID before excessive bleeding had started. Future studies that include platelet function testing in dogs with *A. vasorum* infection would be interesting to further characterize the primary hemostasis in these patients.

Another mechanism for the bleeding is an abnormal secondary hemostasis. In most dogs, one or several coagulation times were prolonged, even though only mildly, consistent with coagulation factor deficiency. Pulmonary thrombosis alone would not explain factor deficiency, as indicated above. Disseminated thrombosis, i.e. disseminated intravascular coagulation (DIC), was proposed as possible cause (Ramsey et al., 1996; Schmitz and Moritz, 2009; Adamantos et al., 2015). Disseminated intravascular coagulation is a dynamic process, and overt bleeding is typically observed in the acute phase. Coagulation tests are quite variable and can change over time. In the acute phase PT, PTT and TT may be normal to increased, fibrinogen concentration may be markedly decreased, normal or increased, and D-dimers would be expected to be elevated (Levi et al., 2009; Rudloff and Kirby, 2014; Kander et al., 2016). Acute DIC may explain at least in part the bleedings in the dogs of this case series. Considering the generally guarded prognosis in dogs with overt DIC, it is still somewhat surprising that several dogs had survived their bleeding for a prolonged period of time without appropriate treatment. If these dogs had DIC, indeed, one possible explanation may be the observation that spontaneous improvement of vascular lesions occurs in *A. vasorum* infection (Prestwood et al. 1981).

Finally, in addition to abnormalities in primary or secondary hemostasis, hyperfibrinolysis has been suggested as another possible mechanism (Zoia and Caldin, 2015). Clinico-pathologically, hyperfibrinolysis would present similar to DIC, with mild prolongations of coagulation times, elevated D-dimers, and low fibrinogen concentration. Hyperfibrinolysis is best diagnosed by viscolelastic testing such as thromboelastometry (Rotem) (Vorweg et al. 2001; Lier et al., 2013). So far, hyperfibrinolysis has been described in one dog with *A. vasorum* infection using thromboelastography (TEG) (Schmitz and Moritz, 2009). A recent study reported TEG results in 30 dogs, however, this study did not conclusively prove the presence of hyperfibrinolysis (Adamantos et al., 2015). At any rate, in view of quite variable results of platelet numbers, coagulation times, fibrinogen and D-Dimer concentrations in dogs bleeding due to *A. vasorum* infection, various mechanisms, including iatrogenic actions, probably play a pathogenetic role.

Whether thrombosis/DIC or hyperfibrinolysis is the most important underlying mechanism in the individual dog diagnosed with *A. vasorum*, has some therapeutic importance. If pronounced disseminated thrombosis is the primary mechanism, attempts at inhibiting further thrombosis and simultaneously providing fresh coagulation factors are the suggested approach. In contrast, if hyperfibrinolysis is an important mechanism, an antifibrinolytic drug like tranexamic acid is the most appropriate treatment. There is a theoretic caveat concerning the use of this drug in *A. vasorum* infection. By its mode of action, and shown in an experimental dog model, tranexamic acid favors pulmonary thrombosis (Moser et al. 1991). Some degree of pulmonary thrombosis is invariably present in dogs infected with *A. vasorum*, and in some may be the cause of heart failure and death (Matos et al. 2016). Ideally, at the time of diagnosis the presence of hemodynamically important pulmonary thrombosis and associated PH is non-invasively evaluated by echocardiography. In the dogs of this series, tranexamic acid was given in 6 cases as part of the treatment, and discernible pulmonary thrombosis was not an apparent complication in any. In people, the use of tranexamic acid is strongly advised in cases of severe traumatic bleeding, even if hyperfibrinolysis is not documented (Roberts, 2015).

In conclusion, *A. vasorum* infection should be considered in the differential diagnosis in dogs presented with unexplained or severe bleeding.

## Limitations of the study

It is not possible to prove that all bleedings in these dogs at each time point were caused by *A. vasorum*, particularly in the dogs that already had shown bleeding months before diagnosis. However, no other explanation was found in any of these dogs, and all survivors remained free of clinical signs after initiating therapy.

## Acknowledgements

The authors gratefully acknowledge the referring veterinarians and the colleagues of the Clinic for Small Animal Internal Medicine, Vetsuisse Faculty University of Zurich, for their contribution of cases.

## Saignements inexplicables comme symptôme clinique primaire chez des chiens souffrant d'une infestation à *Angiostrongylus vasorum*

Un saignement inexplicable a été le symptôme clinique primaire chez 15 chiens chez lesquels une infestation à *A. vasorum* a été diagnostiquée par la suite. Ces saignements ont été observés sous forme d'hémorragies dans la gueule, de saignements externes, de gros hématomes sous-cutanés, d'hémoptysie, de saignements cérébraux, de saignements abdominaux après ovariectomie, de saignements dans la chambre antérieure de l'œil ou sur le trachéotube lors d'intubations. Chez 8 chiens, on a supposé que le saignement était initialement dû à un petit traumatisme ou à une complication opératoire et diverses mesures chirurgicales ont été prises pour résoudre le problème. Chez trois chiens, des symptômes respiratoires ont été observés avant que le saignement n'amène à l'envoi dans un centre de référence. Le temps moyen écoulé entre les premiers symptômes causés par *A. vasorum* et le diagnostic était de 2 semaines (1 jour à 4 mois). Quatre chiens sont décédés, 3 le jour de leur arrivée et un 4 jours plus tard. Les causes probables de la mort étaient dans deux cas une déficience respiratoire et dans deux une hémorragie cérébrale. Quatre chiens avaient été traités précédemment avec des AINS; deux d'entre eux ont développé une hémoptysie massive et un en est mort, un chien a présenté une hémorragie cérébrale fatale et le dernier a développé un volumineux hématome sous-cutané avec une anémie massive. Un saignement à un endroit quelconque peut être la seule anomalie constatée lors d'une infestation par *A. vasorum*. Si on n'a pas d'importants soupçons de cette affection, le diagnostic et le traitement adéquat peuvent être tellement retardés qu'une issue fatale survient. La cause pathophysiologique des hémorragies est vraisemblablement multifactorielle.

## Emorragia inspiegabile come condizione clinica primaria in cani affetti da un'infezione da *Angiostrongylus vasorum*

Un'emorragia inspiegabile era la prima causa clinica in 15 cani con una successiva diagnosi di infezione da *A. vasorum*. Queste emorragie sono state osservate nella cavità orale come emorragia esterna, come esteso ematoma sottocutaneo, come emottisi, come emorragia cerebrale, intraddominale dopo una ovariectomia, come epistassi, nella camera anteriore oculare e nell'intubazione tracheale. In 8 cani, la causa dell'emorragia iniziale sospettata era un piccolo trauma o una complicazione chirurgica. L'eliminazione del problema si è ottenuto dopo diversi interventi chirurgici. Solo in 3 cani sono stati notati sintomi respiratori prima che l'emorragia abbia portato ad una visita specialistica. Il tempo medio trascorso tra la prima anomalia clinica causata da *A. vasorum* fino alla diagnosi era di 2 settimane (da un giorno a quattro mesi). Quattro cani sono deceduti, 3 il giorno dell'ammissione in clinica e 1 quattro giorni dopo l'ammissione. Le cause del decesso sospettate erano insufficienza respiratoria e emorragia cerebrale su ciascuno dei 2 cani. Quattro cani sono stati pretrattati con un NSAIA; di questi 2 hanno sviluppato una grave emottisi (1 deceduto), 1 cane ha sviluppato una emorragia cerebrale (ed è deceduto), e 1 cane ha sviluppato un ampio ematoma sottocutaneo con grave anemia. Un'emorragia in un qualsiasi punto può essere l'unica anomalia clinica di una infezione da *A. vasorum*. Senza un forte sospetto della malattia, la diagnosi e il trattamento adeguato possono essere talmente protratti da portare a un esito letale. Le cause fisiopatologiche dell'emorragia sono probabilmente multifattoriali.

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